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Validation and quantitation of human biomarkers using accelerator mass spectrometry

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Establishing and quantifying exposure of individuals to environmental carcinogens/mutagens requires a knowledge of the compounds' biotrans-formation pathways. This information is often obtained from animal models in which high doses of the compound are administered and extrapolations made to low-dose exposure. This approach takes no account of species differences in metabolism and hence we may be under- or over-estimating risks. To date, it has not been possible to ethically administer carcinogens/mutagens to humans due to the insensitivity of our analytical procedures. This situation has been radically altered by the development of the technique of accelerator mass spectrometry (AMS). This nuclear physics procedure permits one to measure isotopes with high sensitivity (attomole to zeptomole amounts). We have used AMS to measure the biotransformation and macromolecular adduct formation of a number of dietary carcinogens in both animal models and humans. Carcinogens examined include (i) the human carcinogen aflatoxin B1 and its less potent analogue aflatoxin B2; (ii) the heterocyclic amine food mutagens MeIQx and PhIP; and (iii) the polycyclic aromatic hydrocarbons benzo(a)pyrene and pyrene. Each of these compounds appears to have different patterns of metabolism in humans compared to rats. In the case of MeIQx and PhIP these differences are substantial; humans forming more of the activated species than rats as well as forming higher adduct levels. The implications of these results will be discussed in relation to human carcinogen/mutagen risk assessment.